Alpha Thalassemia Fact Sheet

Thalassemia

Thalassemias are a group of disorders which have in common the inability to produce sufficient quantities of globin chains necessary for hemoglobin synthesis. The most common types of thalassemias are alpha and beta, which are named according to the type of chain affected. The focus of this material is alpha thalassemia.

Alpha Thalassemia

There are four genes which code for alpha chain production. Alpha thalassemia results when one or more of these genes are not working. The number and location of the non-working genes determines the type of alpha thalassemia an individual has.

Types of Alpha Thalassemia

Alpha thalassemia major (Hydrops Fetalis): Deletion of all four alpha globin genes. No alpha chains, which are necessary for the formation of fetal hemoglobin, are produced. Death usually occurs in utero or early infancy. Treatment consists of ongoing transfusions.

Hemoglobin H (Hb H) disease: Deletion of three alpha globin genes. The clinical complications associated with Hb H disease are variable. This generally results in mild to moderate anemia, and is often associated with microcytosis, hypochromia, and red cell fragmentation.

Hemoglobin H is an abnormal hemoglobin found in people with alpha thalassemia. When three or more alpha globin genes malfunction, there is an excess of beta globin chains. The excess chains create unstable tetramers called hemoglobin H. The tetramer of beta globin chains (4β) forms when there are insufficient alpha (α) chains to make normal adult hemoglobin (2α, 2β). The fetus manufactures gamma (γ) chains rather than β chains, and the tetramer of γ chains that forms is called hemoglobin Barts (4γ). During the newborn period, when gamma globin production is still high and beta globin production is low, the gamma chains form the unstable tetramers identified as hemoglobin Barts. However, Hb Barts decreases with the normal decrease in gamma chain production and therefore, over time, it disappears and is replaced by Hb H. These unstable tetramers eventually precipitate in the red blood cells, causing membrane damage and premature destruction of the cells producing a chronic hemolytic anemia. It is the identification of large amounts of Hb Barts that leads us to presume the infant will have Hb H disease. DNA testing is necessary to make the final diagnosis.

Hemoglobin H (Hb H)-Constant Spring disease: Deletion of two alpha globin genes and a point mutation of a third. This is generally a more severe form of Hb H disease, usually with a moderate to severe clinical course. Complications include the development of splenomegaly and cholelithiasis. Some individuals may require intermittent to chronic transfusions.

Clinical symptoms for both forms of Hb H disease that can begin at birth include pallor and jaundice. In addition, severe anemia may be caused by certain types of medications (including aspirin, sulfa drugs, some antibacterials) as well as fava beans and mothballs. Avoidance of these substances is recommended. (For a more detailed list of substances to avoid, please see the NBS booklet called *For Parents of Babies with Hemoglobin H Disease*.)

Alpha thalassemia trait (also called alpha thalassemia minor): Deletion of two alpha globin genes. This condition is clinically benign. The clinical manifestations include microcytosis and mild, if any, anemia, which is often confused with iron deficiency anemia. However, unless the individual also has iron deficiency anemia, iron supplementation is usually not recommended. People with alpha thalassemia trait may be at risk for having a child with hemoglobin H disease or alpha thalassemia major.

Alpha thalassemia "silent carrier": Deletion of one alpha globin gene. This condition is clinically benign, usually with no clinical manifestations.

The California Newborn Screening Program

Clinically significant hemoglobinopathies currently identified by the Newborn Screening (NBS) Program include sickle cell disease (sickle cell anemia, sickle hemoglobin C, sickle hemoglobin D, sickle hemoglobin E, and sickle Beta thalassemia), $Beta^0$ thalassemia, and hemoglobin E/Beta thalassemia. On October 28, 1999 the NBS Program expanded to identify hemoglobin H (Hb H) disease including the more severe form of this disorder Hb H-Constant Spring disease. Additionally, alpha thalassemia major can be identified if a NBS sample is obtained. Because of the conservative cutoff for Hb H disease, a small number of alpha thalassemia traits will also be identified.

In the fall of 1996 the NBS Program began conducting a pilot Hb H screening project. The goals of this project were to determine how reliably hemoglobin Barts can be detected using our high performance liquid chromatography (HPLC) screening method and to determine the feasibility of establishing a reasonable cutoff for Hb H disease. It was learned that a peak at the origin of the hemoglobin pattern correlates reliably with hemoglobin Barts. We arrived at a presumed Barts cutoff of 25% in this "fast window" of the chromatogram. This appears to detect most of the cases of hemoglobin H disease while minimizing the number of false positives for disease, which are actually two gene deletion cases, a clinically benign carrier condition known as alpha thalassemia trait.

We are reporting all cases at and above the 25% cutoff. They are followed as are other hemoglobin disorders. Confirmatory testing including DNA is provided and referral to a California Children's Services (CCS) Sickle Cell Disease/Hemoglobinopathies Center is strongly recommended. As a result of the pilot project, we anticipate that approximately one-third of the Hb H cases will be the more clinically serious Hb H/Constant Spring Disease. Newborn Screening Coordinators at Area Genetic Centers across the State will assist with referrals to CCS Centers.

The presence of presumed hemoglobin Barts below the cutoff is ***not*** noted on the NBS results mailer, nor is follow-up provided. Most infants with alpha thalassemia trait will have fast hemoglobin below the 25% cutoff and therefore will not be identified through the NBS Program. Furthermore, while samples were tested as low as 15% during the pilot project without identifying a presumed case of Hb H disease between the 15 – 25% range, you should be aware that we have not eliminated the possibility that cases of hemoglobin H disease could have fast hemoglobin percentages below the 25% cutoff. **As with all population based screening, it is possible that a newborn with Hb H disease could have a percentage of "fast" hemoglobin below the cut-off and therefore not be reported.**